Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Thompson MG, Burgess JL, Naleway AL, et al. Prevention and attenuation of Covid-19 with the BNT162b2 and mRNA-1273 vaccines. N Engl J Med. DOI: 10.1056/NEJMoa2107058

Supplementary Material

Contents

A. Acknowledgements

On behalf of HEROES-RECOVER Network , we thank Al Barskey, Lenee Blanton, Christopher Braden, William Brannen, Joseph Bresee, Erin Burns, Joanne Cono, Gordana Derado, Jill Ferdinands, Anthony Fiore, Katherine Garvin, Jacqueline Gindler, Susan Goldstein, Luis Rivera Gonzalez, Brendan Flannery, Aron Hall, Lauri Hicks, Pellumbeshe Hoxhaj, Douglas E. Jordan, Zoe Kaplan, Pam Kennedy, Brian A. King, Archana Kumar, Adam J. Langer, Jennifer Layden, Brandi Limbago, Adam MacNeil, Elissa Meites, Andrea McCollum, L. Clifford McDonald, Christina McMichael, Natalie Olson, Todd Parker, Palak Patel, Mary Reynolds, Sue Reynolds, Stephanie Schrag, Nong Shang, Abigail Shefer, Alan Sims, Robert Slaughter, Dylan Sorensen, Matthew J. Stuckey, Robert V Tauxe, Natalie Thornburg, Vic Veguilla, Jennifer Verani, Katherine (Leza)Young, Rose Wang, Bao-Ping Zhu, CDC; Genesis Barron, Cynthia Beaver, Dimaye Calvo, Esteban Cardona, Adam Carl, Andrea Carmona, Alissa Coleman, Zoe Baccam, Emily Cooksey, Stacy Delgado, Kiara Earley, Ryan Ejindu, Natalie Giroux, Sofia Grijalva, Allan Guidos, Brad Haeckel, Adrianna Hernandez, James Hollister, Theresa Hopkins, Christina Hughey, Rezwana Islam, Gabriella Jimenez, Krystal Jovel, Olivia Kavanagh, Karla Ledezma, Jonathan Leyva, Sally Littau, Amelia Lobos, James Lopez, Paola Louzado Feliciano, Michael Johnson, Elizabeth Kim, Kenneth Komatsu, Veronica Lugo, Jeremy Makar, Taylor Maldonado, Enrique Marquez, Allyson Munoz, Janko Nikolich, Sandrai Norman, Assumpta Nsengiyunva, Kennedy O'brien, Joel Parker, Jonathan Perez Leyva, Alexa Roy, Katerina Santiago, Carlos Silvera, Saskia Smidt, Isabella Terrazas, Tahlia Thompson, Heena Timsina, Erica Vanover, Graham Wegner, Mandie White, April Yingst, University of Arizona, Arizona Department of Health Services, University of Miami; Yolanda Prado, Daniel Sapp, Mi Lee, Chris Eddy, Matt Hornbrook, Danielle Millay, Dorothy Kurdyla, Ambrosia Bass, Kristi Bays, Kimberly Berame,

Cathleen Bourdoin, Carlea Buslach, Kenni Graham, Tarika Holness, Abreeanah Magdaleno, Joyce Smith-McGee, Sam Peterson, Aaron Piepert, Krystil Phillips, Joanna Price, Sperry Robinson, Katrina Schell, Emily Schield, Natosha Shirley, Anna Shivinsky, Britta Torgrimson-Ojerio, Shawn Westaway, Kaiser Permanente Northwest; Angela Hunt, Jessica Lundgreen, Karley Respet, Jennifer Viergutz, St. Luke's; Camie Schaefer, Arlyne Arteaga, Matthew Bruner, Daniel Dawson, Emilee Eden, Jenna Praggastis, Joseph Stanford, Jeanmarie Mayer, Marcus Stucki, Jonathan Thibaudeau, Riley Campbell, Kathy Tran, Madeleine Smith, Braydon Black, Christina Pick, Madison Tallman, Chapman Cox, Derrick Wong, Michael Langston, Adriele Fugal, Fiona Tsang, Maya Wheeler, Gretchen Maughan, Alexis Lowe, University of Utah; Jake Andreae, Adam Bissonnette, Krystal Boese, Michaela Braun, Cody DeHamer, Timothy Dziedzic, Joseph Eddy, Heather Edgren, Wayne Frome, Nolan Herman, Mitchell Hertel, Erin Higdon, Rosebud Johnson, Steve Kaiser, Tammy Koepel, Sarah Kohn, Taylor Kent, Thao Le, Carrie Marcis, Megan Maronde, Isaac McCready, Nidhi Mehta, Daniel Miesbauer, Anne Nikolai, Brooke Olson, Lisa Ott, Cory Pike, Nicole Price, Christopher Reardon, Logan Schafer, Rachel Schoone, Jaclyn Schneider, Tapan Sharma, Melissa Strupp, Janay Walters, Alyssa Weber, Reynor Wilhorn, Ryan Wright, Benjamin Zimmerman, Marshfield Clinic Research Laboratory; Andrea Bronaugh, Tana Brummer, James Carr, Claire Douglas, Michael Duckworth, Kate Durocher, Hala Deeb, Rebecca Devlin, Sauma Doka, Tara Earl, Jini Etolue, Deanna Fleary, Jessica Flores, Chris Flygare, Isaiah Gerber, Louise Hadden, Jenna Harder, Katherine Harris, Don LaLiberty, Lindsay LeClair, Nancy McGarry, Peenaz Mistry, Steve Pickett, Brandon Poe, Khaila Prather, David Pulaski, Rajbansi Raorane, Meghan Shea, Nicole Simmons, Brian Sokol, John Thacker, Matthew Trombley, Pearl Zheng, Chao Zhou, Abt Associates; Alejandro Arroliga, Madhava Beeram, Todd Crumbaker, Thomas Denton, Jason Ettlinger, Angela Kennedy, Mary

Kylberg, John Myers, Binitha Rajapudi, Spencer Rose, Natalie Settelie, Rupande Patel, Jennifer Thomas, Baylor Scott & White Health; HEROES-RECOVER cohort participants

Supplementary Appendix Methods

B. Protocol Methods for HEROES and applicable to both HEROES and RECOVER cohorts

The HEROES-RECOVER network consists of the Arizona Healthcare, Emergency Response and Other Essential Workers Surveillance (HEROES) study and the Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel (RECOVER) study. An overview of the HEROES study protocol and procedures is available in a pre-publication: h**ttps://pubmed.ncbi.nlm.nih.gov/34057904/**

The text below describes the HEROES protocol; however, these methods are consistent with the RECOVER study.

Participants

Eligibility Criteria

Eligible participants include Arizona residents aged 18–85 years who currently work at least 20 hours per week in an occupation involving regular direct contact (within three feet) with others, assessed at the participant level. We have intentionally chosen a broad occupational category for essential workers in order to capture the full breadth of occupations where an employee cannot socially distance to conduct their work.[1] The occupations are categorized as Health Care Personnel (HCP), First Responders (FR), or Other Essential Workers (OEW). HCP include clinical providers and support staff in inpatient, outpatient, or residential settings. FR include firefighters, emergency medical services, law enforcement, border patrol, and correctional officers. OEW include workers in the following sectors: education, agriculture and food processing, public and other transportation services, solid waste collection, warehouse and delivery, utilities, government and community-based services, childcare, information technology,

environmental services, and hospitality. All participants must have access to a smartphone or internet-connected computer, a mailing address, and ability to speak or write English or Spanish. Exclusion criteria include receipt of a COVID-19 vaccine prior to enrollment, although we continue to follow participants who are vaccinated during the study. The majority of the cohort's HCP and FR were recruited prior to COVID-19 vaccine availability.

Recruitment Strategy

In order to enroll 4000 participants as quickly as possible, we employed a multipronged recruitment strategy. First, we recruited from ongoing Arizona-based COVID-19 testing activities, such as university-driven antibody and saliva testing initiatives and occupation-based state health department surveillance. Second, we partnered with community-based COVID-19 studies to recruit from ongoing COVID-19 population cohorts. Third, the study accepts self-referrals, so we have developed a marketing strategy to increase general study awareness through press releases and targeted recruitment to the specific occupation groups.

All recruitment and enrollment activities were conducted remotely utilizing a virtual call-center platform and REDCap[2] to ensure staff and participant safety. Direct recruitment was conducted via phone and email. Interested participants were given the option to complete a self-screening questionnaire emailed to them, or to complete a screening interview over the phone. Once deemed eligible for the study, participants receive an electronic consent by email to review and sign electronically through REDCap.

Sampling targets were based upon the employment demographics of Arizona. We sought to enroll essential workers in the following proportions: 50% from 18–40 years old and 50% between 41 and 85 years; 50% women; 50% Hispanic or American Indian. By occupation, we sought to enroll 40% HCP, 30% FR, and 30% OEW. These sampling breakdowns are presented

for every 1000 participants in Table 2. Our goal was to enroll these proportions in both seronegative and seropositive participants (Table 2). As specified targets were met, recruitment and enrollment priorities shifted to under-enrolled groups.

Enrollment

Upon enrollment, participants were asked to complete a baseline questionnaire which collected information about sociodemographic characteristics, health status and behaviors, occupational exposure (tailored to the occupational category), history with and attitudes about COVID-19, and influenza vaccination history during the 2020–21 influenza season and the previous five seasons (Table 3). Participants were asked to schedule a blood draw within five days of enrollment at a laboratory facility in their area. This sera sample was used to examine their baseline serology. Finally, participants were shipped a box of self-collection respiratory specimen kits so they can begin active surveillance.

Active Surveillance

As part of active surveillance for incident SARS-CoV-2 infection, all participants provided weekly self-collected mid-turbinate nasal swabs appropriate for testing of SARS-CoV-2 and influenza (during influenza season). At the conclusion of the study, participants will have provided between 36 weeks to two years of weekly self-collected respiratory specimens. Study staff prepared and distributed self-collection kits to the study participants, including detailed paper and video instructions for collection. If an individual experienced COVID-19–like illness (CLI), they were asked to collect an additional respiratory specimen on the date of first CLI symptom onset. Specimen collection supplies for the weekly and CLI kits were differentiated by color so participants know which to use and study staff can track supplies. Respiratory specimens were analyzed utilizing the CDC-designated reference laboratory for real-time reverse

transcription polymerase chain reaction (RT-PCR) assay testing. The laboratory provided feedback on specimens that were unable to be tested because of participant error in collection or issues with shipping the sample (e.g., leaking or missing required components). The feedback was then utilized to re-educate participants on specimen collection and shipping procedures. If participants received a positive SARS-CoV-2 test result, trained study staff contacted participants to provide CDC guidance on quarantine practices and warning signs requiring medical care and to answer any questions they have.

Enrolled cohort members also participated in active surveillance via weekly surveys, explained in detail in the Data Collection section.

Data Collection

Active surveillance for acute illness was conducted throughout the study period. Participants were prompted to begin surveillance in the week following study enrollment and completion of the baseline questionnaire. Each week, all participants were contacted via text message on their predesignated surveillance day (described in detail below). At the end of each text message exchange, the participant was reminded to collect a weekly specimen on their assigned day for collection.

Active Surveillance Surveys

As a part of active surveillance, participants were contacted weekly via secure short message service (SMS) text messages (via Twilio) asking them two standardized questions about their general health status and presence of CLI symptoms. Twilio is a text-messaging service that can read/write into the study REDCap database and customize questions based upon participant responses. In addition to the two standardized questions, participant received one of four sets of rotating questions each week about changes in their occupational SARS-CoV-2 exposure,

community and household exposure, and attitudes and beliefs surrounding COVID-19 risk. Any individual who indicated CLI in a weekly survey, or contacted study staff directly, answered additional questions via a mobile-friendly webform to ascertain the participant's symptoms, self-reported severity, duration, self-reported medical treatment, during- and post-illness function, and details about the resolution of their illness.

Self-Reported Data

Participants who indicated they had experienced CLI in the last seven days were then moved to an acute illness monitoring flow where they were instructed to collect and ship an acute illness specimen and complete additional questions about their illness episode. Individuals could also be placed into the acute illness monitoring flow by notifying study staff that they are experiencing CLI. Participants remained in the acute illness arm of active surveillance until they self-report that their illness has resolved. Before returning to the weekly active surveillance flow, participants completed a recovery survey in which they confirmed duration of illness and answered questions about atypical symptoms, productivity loss, and use of health services. Participants continued to collect weekly respiratory specimens throughout their acute illness monitoring.

Vaccine Information

Participants were asked a series of questions to assess their knowledge, attitudes, and practices (KAP) related to COVID-19 vaccination in the baseline and/or follow-up survey in order to capture the information prior to vaccination. Similar to previous KAP studies of influenza vaccines,[3,4] participants were asked how much they know about the COVID-19 vaccines, if they received the vaccine, their intention to receive one if they have not already, how

safe and effective they think the vaccines are, and how likely they are to get sick if they do not receive a vaccine.

As soon as one or multiple COVID-19 vaccines were made available to individuals within the study, they were prompted about vaccine intent and asked to text “vaccine” to the SMS platform if/when they got vaccinated. Once vaccinated, they completed a brief webform on date of vaccination, vaccine manufacturer and order in sequence for vaccines requiring multiple doses (e.g., first or second dose). State Immunization Information System registries were used as a backup to capture vaccine information about individuals who did not share the information with the study via text message, and for confirmation and completeness on individuals who did receive it.

Laboratory Methods

Respiratory specimens. Participants were asked to self-collect a respiratory specimen each week of the study period. Sampling kits were provided to all study participants, which included collection and shipping supplies for eight weeks of collection, along with illustrated instructions on how to properly collect and ship thee respiratory specimens. Study staff track the use of specimen kits and ship replenishments to participants as needed. Each week, regardless of symptoms, participants collected an anterior mid-turbinate nasal swab on both nares using a flocked swab or equivalent and placed it into a tube containing viral transport media (VTM). If participants experience CLI, they used an ‘acute illness kit’ which consisted of materials to collect a nasal swab in VTM and a saliva specimen in a saliva-collection tube without stabilixin. All specimens were shipped with a cold pack, using priority overnight express shipping to a CDC-designated laboratory following International Air Transport Association (IATA) guidelines.[5] Upon receipt by the laboratory, specimens were aliquoted and analyzed for SARS-

CoV-2 using a RT-PCR method[6] under FDA emergency use authorization (EUA). Remaining aliquots were maintained for additional analysis, banking or long-term storage.

Blood specimens. All participants contributed whole blood at enrollment, at 11- to 13-week intervals, following a positive SARS-CoV-2 RT-PCR test (convalescent specimen), and following receipt of a COVID-19 vaccine (Figure 1). Participants could submit specimens at participating laboratories closest to the participant's residence or work. If a participant did not develop symptoms, but SARS-CoV-2 was detected in a weekly specimen, participants were instructed to submit a blood sample approximately four weeks following the date of first RT-PCR detection; if the participant experienced CLI within two weeks of virus detection, they were instructed to submit a blood sample four weeks after initial symptom onset. If the participant had a convalescent blood specimen drawn prior to another planned repeat blood collection, the scheduling of following blood collections were 11–13 weeks following the convalescent draw. Participants who receive the COVID-19 vaccine during the study period were asked to provide a blood specimen at 14–21 days after each dose of the vaccine (with the first post-vaccination blood draw collected prior to the second vaccination dose, if relevant), and then every 11–13 weeks as described above. Information on adverse events and symptoms related to vaccination were collected retrospectively after participants received both doses of the vaccine.

Whole blood was collected and processed using CDC guidelines for serum collection.[7] All specimens were stored at -70 degrees C or colder prior to SARS-CoV-2 antibody analysis or long-term storage. At the University of Arizona, the serum was tested for antibodies against the receptor binding domain (RBD) of the spike protein and verified with the S2 domain of S protein antibodies, as previously described,[8] using the FDA EUA (ID#201116) test. This testing at study

entry was used to ensure correct placement of AZ HEROES participants into seronegative or seropositive groups.

Data Collection and Security

Most research activities occurred through electronic communications (email, text, and internet-based surveys), telephone contacts, or via postal or express mail, minimizing direct contact between study staff and participants. All surveys were self-administered by participants on a computer or smartphone. Surveys could also be administered by telephone or mail should participants be unable or become unwilling to access them online. Participant information given to study staff via phone or email conversation was entered and stored in REDCap by study staff. Alternatively, data were imported into REDCap directly from Twilio following participant response to text surveillance or via direct participant response within a survey in REDCap.

Data Management

REDCap. A study database was maintained in REDCap. Tracking databases with patient identifiers and contact information were kept securely according to the University of Arizona standard operating procedures with respect to cybersecurity, privacy, patient confidentiality, and compliance with applicable patient privacy regulations. Any study-related documents with personal identifiers were stored in a locked cabinet in lockable offices on campus. All study-related documents and specimens contained a unique identifier for each participant. Data entry forms provided some quality assurance using logic and range checks and automated skip patterns. The research team performed additional data quality checks on a weekly basis, including assessments of missing data. Laboratory results were entered directly into the REDCap study database from the study reference laboratory, including results from RT-PCR assays and

serologic assays. If a reference laboratory was not able to enter data directly, the laboratory was provided a laboratory results reporting template that was then merged with study data.

Twilio. Twilio is a cloud-based communications platform that allows for automated text messaging chains to be sent to study participants. It was used to send weekly and illness monitoring questions to participants. Participant responses were stored in Twilio until sent as a batch to REDCap once per day.

Statistical Considerations

Power Analysis. Our goal was to recruit 4000 participants, split evenly between seronegative and seropositive individuals. Among the seronegative cohort, we estimated a sample of >852 was required to achieve 80% power (alpha = .05) to detect a true incidence of SARS-CoV-2 infection of 4% (and the enrolled cohort exceeds this sample estimate at the drafting of this report).We expect to be sufficiently powered to make overall estimates and estimates by two-level-strata (such as age, sex, or healthcare personnel vs. others). Power estimation for COVID-19 vaccine effectiveness (VE) was performed using Monte Carlo simulation to generate survival time over 12-months based on varying vaccine coverage (with quarterly increases in 2-dose vaccine coverage from 0% to 80% among HCP, 70% for FR, and 30% for OEW) and varying SARS-CoV-2 incidence rate (from 0.67% to 1.42% monthly attack rate) using the equations proposed by Austin and a Cox marginal model.[9] Based on 1000 simulations, with 2000 participants in the seronegative stratum, the study is estimated to have >80% power to detect a true vaccine effectiveness (VE) of 75%. If the data are pooled with similar studies using common methodologies to a total of 5000 participants, the combined analysis is estimated to have 99% power to detect a true VE of 75% using the same assumptions.

Data analysis. To estimate the incidence of SARS-CoV-2 infection and the corresponding 95% confidence intervals in essential workers, we will fit negative binomial regression models to the data stratified by RT-PCR-confirmed infections, occupation, symptom presentation, close contact exposure, and demographic variables, with follow-up time as an offset. Logistic regression and negative binomial models will be used to estimate the risk of infection in different occupational groups. In the logistic regression model, we will include the log-transformed person weeks as the offset. The model is then adjusted by symptom presentation, demographic factors, study site, and healthcare utilization. The VE (1 − confirmed cases of COVID-19 illness per 1000 person-weeks among vaccinated essential workers ÷ confirmed cases of COVID-19 illness per 1000 person-weeks among unvaccinated essential workers × 100%) with 95% confidence intervals will be estimated by a negative binomial regression model. The potential confounders such as study site and previously seropositive status will be included in the model. We will apply nonlinear mixed models to describe individual and group mean trajectories in neutralizing antibody titers over time. We will classify and identify subgroups of cases by self-reported clinical severity, healthcare utilization, occupational and community exposures, and duration of symptoms. These models will help elucidate the patterns of serologic immunity.

Ethical Considerations

The HEROES study protocol was reviewed and approved by the University of Arizona and the Arizona Department of Health Services (ADHS) Institutional Review Board (IRB).[1] The ADHS IRB approved the study and the CDC IRB deferred to the University of Arizona IRB. The

[1] § See 45 C.F.R. part 46.114

college of public health at the University of Arizona houses all IRB and required study documentation. All participants completed informed consent electronically through the REDCap study database. Research staff verified participants understood key study activities, were aware of risks, and agreed to participate prior to countersigning to confirm consent. Participants received the results of their weekly and illness SARS-CoV-2 RT-PCR tests as well as the results of their antibody testing.

C. Vaccination Status Documentation

The 796 unvaccinated participants in Table 1 includes 39 participants who received the Johnson & Johnson COVID-19 vaccine. These participants contributed unvaccinated person-days to the analysis and were censored starting on the date of vaccination. Of the remaining 757 unvaccinated participants, 689 (91.0%) were confirmed as unvaccinated by multiple methods, including electronic or telephone surveys (at all study sites) and reviews of electronic medical and occupational records and/or state immunization registries at sites in Minnesota, Oregon, Texas, and Utah. The remaining 68/757 (9.0%) were at the Arizona or Florida study sites and could not be reached for confirmation. They were presumed to be unvaccinated but were removed from VE estimates in a sensitivity model described below.

D. Laboratory Real-time RT-PCR

RNA extraction was performed using the MagMAX Viral/Pathogen Nucleic Acid Isolation Kit on the KingFisher Flex system. RT-PCR was performed using the TaqPath™ COVID-19 Combo Kit on the QuantStudio 7 Pro real-time RT-PCR system. Positive specimens were defined as having at least two SARS-CoV-2 targets (ORF1ab, N gene, S gene) with a threshold cycle (Ct) value ≤37 per manufacturer's instructions.[10] Approximately 20% of specimens were randomly selected for re-testing as part of routine quality control testing procedures.

E. Laboratory: Quantitative SARS-CoV-2 RT-PCR

Residual positive specimens from the Marshfield Clinical Research Institute were frozen at -70 degrees C and shipped on dry ice to the Wisconsin State Laboratory of Hygiene (WSLH) for quantitative SARS-CoV-2 RT-PCR. At the WSLH, specimens were extracted using a QIAcube HT with QIAmp 96 Virus extraction kit (PN 57731) and run on an ABI 7500 Fast Dx using the CDC Influenza SARS-CoV-2 (Flu SC2) Multiplex Assay

(https://www.fda.gov/media/139743/download). The SARS-CoV-2 and RNase P targets from this multiplex assay were utilized, and the influenza A and influenza B targets were not analyzed. This assay has Emergency Use Authorization as a qualitative real-time RT-PCR test. To make this assay into a quantitative test, a standard curve of synthetic SARS-CoV-2 RNA (PN 102024, Twist Bioscience) was included on every ABI 7500 run. Starting with 1E+6 copies/µl, a six-point standard curve of 10-fold dilutions were included on each RT-PCR run, with each dilution run in triplicate (18 wells total). Each specimen was initially run in triplicate, but, because replicates of each specimen were very similar to each other (Ct Standard Deviation <1), after the first run specimens were tested once (in one well). The average Ct values of each dilution of standard were plotted using linear regression, and the linear regression equation was used to convert Ct values of specimens into log copies/µL for each specimen. Specimens with Ct values outside the standard curve were reported as <10 copies/µL or >1,000,000 copies/µL.

For quality control, one negative control and one quantified positive control (Cat. NATSARS COV2-ERC, Zeptometrix Corp.) were included for each extraction run and for each RT-PCR run. For a run to pass, the negative control must be negative, and the positive control must be within the range of mean+/- 3 standard deviations of the average Ct value of the positive control. In addition, to pass quality control, the R-squared of the standard curve must be >0.97. In reality, the R-squared was consistently ≥0.99. For each specimen to pass, the RNase P Ct needed to be <35, indicating adequate human specimen collection; all specimens passed this minimal indicator of specimen quality.

Genetic sequence of the SARS-CoV-2 target region was analyzed to determine if genetic substitutions may have impacted genome copy calculations in vaccinated infections. No systematic substitutions were seen in the conserved SC2 target region.

F. Laboratory: Genetic Sequencing

Available specimens with <32 Ct value by RT-PCR were subjected to SARS-CoV-2 whole genome sequencing by the Illumina MiSeq platform following previously published protocols.[11] Additional RT-PCR amplicon amplification followed by Sanger sequencing was applied to the samples with incomplete genome sequences after initial Miseq sequencing.[11] Consensus sequences were generated with Iterative Refinement Meta-Assembler (IRMA) (IRMA v1.0.2 with LABEL v0.6.3 for Linux & Mac OS X, 03-2021) and the SARS CoV-2 genome sequence lineage call was based on PANGOLIN v2.3.8 (https://github.com/cov-lineages/pangolin). Lineages were categorized as variants of concern, variants of interest, wild type, or other variants according to criteria published by CDC: SARS-CoV-2 Variant Classifications and Definitions: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html.

Sequencing was conducted on SARS-CoV-2 viruses isolated from 22 participants who were ≥7 days post-vaccine dose one at infection (through March 3 2021) and among 3-4 location- and closest date-matched unvaccinated participants, as available. Due to the very low number of participants with SARS-CoV-2 infection after vaccination and high vaccine uptake among participants, four unvaccinated cases at the same location with infection dates closest to the index case were not always available. A total of 71 unvaccinated participants were identified (**Table S3**).

G. Statistical Analysis Methods

Sample Size and Participant Inclusion

As stated in the synopsis from the HEROES protocol, we achieved sufficient sample size >852 seronegative participants required to achieve 80% power (alpha = .05) to detect a true

incidence of SARS-CoV-2 infection of 4% (and the enrolled cohort exceeds this sample estimate at the drafting of this report). Of 6,168 eligible participants enrolled, 1,046 withdrew or were lost to follow-up prior to December 14, 2020 (**Figure S2**). Withdrawn participants were significantly more likely to be younger, male, not white, Hispanic, and less likely to have a chronic condition (**Table S2**).

Inverse Propensity of Treatment Weighting

Data were divided into weeks and participants were considered immunized if they attained 14 days after vaccination in that week. Baseline covariates in the propensity model included site, sex, age, race, ethnicity, occupation, health status, medical conditions and medications, household characteristics, and influenza vaccination history (**Table S2**).[12] Time varying covariates in the propensity model included study week, local SARS-CoV-2 circulation (percent positive provided by HHS Protect Public Data Hub: https://protect-public.hhs.gov), number of hours worked in contact with patients or the public, number of hours in direct contact with someone with known or suspected COVID-19, and percent of time wearing personal protective equipment (PPE) during each of those exposure categories. Local SARS-CoV-2 circulation reflects the average for each week by site. Exposure and PPE use are updated by participants every three weeks and the weekly data structure reflects updates as they occur. Propensity to be vaccinated was estimated using boosted regression trees. Average treatment effect (ATE) weights were calculated to assess covariate balance before and after weighting using standardized mean differences. The marginal probability of vaccination was estimated with baseline covariates to stabilize the weights. Final stabilized weights had a mean of 0.95 and maximum of 5.55.

Cox Model

Hazard ratios were calculated by the Andersen-Gill model and vaccine effectiveness was then calculated as 100%×(1-hazard ratio). The Andersen-Gill model is a generalized Cox proportional hazard model that defines the risk intervals based on the counting process. By applying the counting process method, it is possible to model time-to-event data that one can contribute multiple risk intervals.[13] Cox models were weighted using the stabilized weights and had site, local SARS-CoV-2 circulation, and occupation as covariates a priori to adjust for any remaining bias. Robust standard errors were used to account for the clustering by participant created by the stabilized weights.

Assumption of Proportional Hazard

The proportional hazards assumption was checked for the main and subgroup Cox models by examining correlation between Schoenfeld residuals and time. No evidence of a non-zero slope was found with $p>0.05$ for all tests.

Vaccine Attenuation and Duration

Attenuation of disease was analyzed among participants with an RT-PCR confirmed infection. We collapsed vaccination exposure into any vaccination due to the small number of breakthrough infections. All analyses compared any vaccination to unvaccinated at the time of illness start. The highest viral RNA loads (Log_{10} copies/mL) measured during RT-PCR-confirmed infection comparisons used a Poisson model. Dichotomous outcomes, PCR positivity for more than one week and febrile illness, used log-logistic regression to calculate relative risks. Comparisons of illness duration outcomes in days were made with Student's t-test assuming unequal variances. Bivariate analyses assessed baseline characteristics, outcomes for potential relationships and use as covariates. The Poisson model for viral load adjusted for days from

symptom onset to specimen collection and for days in transit to the laboratory a priori. Other potential covariates were added independently to each model and kept only if they adjusted the estimate by at least 5%.

Handling of Missing Data

All baseline covariates in the propensity models had complete data. Hours of exposure and percent PPE use were answered by participants when applicable. “Not applicable” was used as a valid response in the boosted regression model and all participant data was used.

VE Sensitivity Analysis

A sensitivity analysis for VE was conducted censoring person-days associated with potential misclassification bias and with periods of low virus circulation. Specifically, VE was calculated censoring person-time for 68 participants missing confirmation that they were unvaccinated (censoring at the date when the first participant achieved partial immunization at that site location) and five participants with an indeterminate RT-PCR result (censoring at the date of symptom onset or collection date for this potentially false negative result). In this model, person-days were also excluded at a study location if local virus circulation fell below 3% for at least five days and there were no RT-PCR-confirmed infections in the cohort (**Table S4).** A circulation threshold of 3%-5% has been used in prior VE studies to define seasonal circulation of vaccine-preventable viruses in multi-site studies.[14] As listed in the Table below, this applied to three study locations; all three renewed contribution to person-time at the onset of a new RT-PCR-confirmed SARS-CoV-2 infection among a participant.

Location	Date reference counties' % positive drops below %3 for ≥5 days	Later date of last study RT-PCR+ and when local positivity drops below 3% [suspension of site person-time]	Date of RT-PCR+ after a site suspension of person-time	Date site person-time starts again after end or break in person-time
Phoenix, AZ	Not occurred	No suspension	N/A	N/A
Tucson, AZ	3/28/2021	3/28/2021	4/5/2021	4/5/2021
Other, AZ	Not occurred	No suspension	N/A	N/A
Miami, FL	Not occurred	No suspension	N/A	N/A
Duluth, MN	2/15/2021	2/15/2021	4/5/2021	4/5/2021
Portland, OR	3/6/2021	3/6/2021	3/30/2021	3/30/2021
Temple, TX	Not occurred	No suspension	N/A	N/A
Salt Lake City, UT	Not occurred	No suspension	N/A	N/A

Table_S1. Comparison of participants included in the vaccine effectiveness analysis population with participants withdrawn or lost to follow up prior to vaccine availability.

	Total Eligible and Consented Participants N (Col%)	VE Analytic Population N (Row%)	Withdrawn or Lost to Follow-up N (Row%)	p-value*
All participants	5021 (100)	3975 (79.2)	1046 (20.8)	
Cohort location				<0.0001
Phoenix, AZ	642 (12.8)	504 (78.5)	138 (21.5)	
Tucson, AZ	1561 (31.1)	1223 (78.3)	338 (21.7)	
Other, AZ	405 (8.1)	291 (71.9)	114 (28.1)	
Miami, FL	355 (7.1)	239 (67.3)	116 (32.7)	
Duluth, MN	491 (9.8)	456 (92.9)	35 (7.1)	
Portland, OR	528 (10.5)	491 (93.0)	37 (7.0)	
Temple, TX	385 (7.7)	302 (78.4)	83 (21.6)	
Salt Lake City, UT	654 (13.0)	469 (71.7)	185 (28.3)	
Sex				<0.0001
Female †	3041 (60.6)	2464 (81.0)	577 (19.0)	
Male	1980 (39.4)	1511 (76.3)	469 (23.7)	
Age (Years)				<0.0001
18-49	3724 (74.2)	2847 (76.5)	877 (23.5)	
≥50	1297 (25.8)	1128 (87.0)	169 (13.0)	
Race				<0.0001
White	4226 (84.2)	3431 (81.2)	795 (18.8)	
Other	795 (15.8)	544 (68.4)	251 (31.6)	
Ethnicity				<0.0001
Hispanic/Latinx	992 (19.8)	685 (69.1)	307 (30.9)	
Other	4029 (80.2)	3290 (81.7)	739 (18.3)	
Occupation ‡				<0.0001
Primary HCP	919 (18.3)	809 (88.0)	110 (12.0)	
Nurses and other allied HCP	1619 (32.2)	1310 (80.9)	309 (19.1)	
First Responders	1161 (23.1)	818 (70.5)	343 (29.5)	
Essential and other frontline	1271 (25.3)	1038 (81.7)	233 (18.3)	
Missing	51 (1.0)	0 (0.0)	51 (100.0)	
Chronic Condition				<0.0001
None§	3623 (72.2)	2728 (75.3)	895 (24.7)	
1 or more	1398 (27.8)	1247 (89.2)	151 (10.8)	

Abbreviations: Vaccine effectiveness (VE), Healthcare personnel (HCP)

*P-values calculated for categorical variables using Pearson's chi-squared test or Fisher's exact test for cells with <5 observations.

† For 58 participants missing biological sex, it was imputed as the more common category, female.

‡ Occupation categories: Primary HCP (physicians, physician assistants, nurse practitioners, dentists), Other allied HCP (nurses, therapists, technicians, medical assistants, orderlies and all others providing clinical support in inpatient or outpatient settings), first responders (FR; firefighters, law enforcement, corrections, emergency medical technicians), essential and frontline workers (EFW; workers in hospitality, delivery, and retail; teachers; all other occupations that require contact within 3 feet of the public, customers, or co-workers as a routine part of their job).

§ For 297 participants, who did not respond to the self-reported question, they were imputed as none, pending further verification.

Table_S2. Extended version of Table 1 with characteristics of participants by percentage with RT-PCR-confirmed SARS-CoV-2 infections and percentage receiving ≥1 dose of messenger RNA COVID vaccine during study period; all variables contributed to immunization propensity weight calculations.

	Unique Participants		SARS-CoV-2 PCR-Negatives		SARS-CoV-2 PCR-Positives			Unvaccinated		Vaccinated with ≥1 Dose		
	N	Col. %	N	Row %	N	Row %	P-value	N	Row %	N	Row %	P-value
All participants [†]	3975		3771	94.9	204	5.1		796	20.0	3179	80.0	
Socio-demographic characteristics												
Cohort location[‡,§]							<0.0001					<0.0001
Phoenix, AZ	504	12.7	461	91.5	43	8.5	‡	105	20.8	399	79.2	
Tucson, AZ	1223	30.8	1148	93.9	75	6.1	‡	274	22.4	949	77.6	
Other, AZ	291	7.3	276	94.8	15	5.2	‡	70	24.1	221	75.9	
Miami, FL	239	6.0	216	90.4	23	9.6	‡	111	46.4	128	53.6	
Duluth, MN	456	11.5	445	97.6	11	2.4		32	7.0	424	93.0	
Portland, OR	491	12.4	486	99.0	5	1.0		44	9.0	447	91.0	
Temple, TX	302	7.6	284	94.0	18	6.0	‡	66	21.9	236	78.1	
Salt Lake City, UT	469	11.8	455	97.0	14	3.0		94	20.0	375	80.0	
Sex							0.0240					<0.0001
Female[‖]	2464	62.0	2349	95.5	111	4.5		423	17.2	2037	82.8	
Male	1511	38.0	1422	93.9	93	6.1		373	24.6	1142	75.4	
Age (Years)							0.5122					0.0051
18-49	2847	71.6	2705	95.0	142	5.0		602	21.1	2245	78.9	
≥50	1128	28.4	1066	94.5	62	5.5		194	17.2	934	82.8	
Race							0.6882					0.0012
White	3431	86.3	3253	94.8	178	5.2		659	19.2	2772	80.8	
Other	544	13.7	518	95.2	26	4.8		137	25.2	407	74.8	
Ethnicity							<0.0001					<0.0001
Hispanic/Latinx	685	17.2	625	91.2	60	8.8		198	28.9	487	71.1	
Other	3290	82.8	3146	95.6	144	4.4		598	18.2	2692	81.8	
Marital status							0.1368					<0.0001
Married	2514	63.2	2375	94.5	139	5.5		437	17.4	2077	82.6	

Other	1461	(	36.8	)	1396	(	95.6	)	65	(	4.4	)		359	(	24.6	)	1102	(	75.4	)	
Occupation																						
Occupation ¶													<0.0001									<0.0001
Primary HCP	809	(	20.4	)	793	(	98.0	)	16	(	2.0	)		45	(	5.6	)	764	(	94.4	)	
Nurses and other allied HCP	1310	(	33.0	)	1244	(	95.0	)	66	(	5.0	)		204	(	15.6	)	1106	(	84.4	)	
First Responders	818	(	20.6	)	745	(	91.1	)	73	(	8.9	)		257	(	31.4	)	561	(	68.6	)	
Essential and other frontline	1038	(	26.1	)	989	(	95.3	)	49	(	4.7	)		290	(	27.9	)	748	(	72.1	)	
Household characteristics																						
Number of bedrooms													0.6762									0.0689
1	222	(	5.6	)	210	(	94.6	)	12	(	5.4	)		55	(	24.8	)	167	(	75.2	)	
2	568	(	14.3	)	545	(	96.0	)	23	(	4.0	)		109	(	19.2	)	459	(	80.8	)	
3	1601	(	40.3	)	1517	(	94.8	)	84	(	5.2	)		322	(	20.1	)	1279	(	79.9	)	
4	1473	(	37.1	)	1395	(	94.7	)	78	(	5.3	)		262	(	17.8	)	1211	(	86.8	)	
Unknown/refused	111	(	2.8	)	104	(	93.7	)	7	(	6.3	)		48	(	43.2	)	63	(	60.6	)	
Other individuals in household													0.0766									0.0002
0	517	(	13.0	)	483	(	93.4	)	34	(	6.6	)		132	(	25.5	)	385	(	74.5	)	
1	1016	(	25.6	)	968	(	95.3	)	48	(	4.7	)		179	(	17.6	)	837	(	82.4	)	
2	882	(	22.2	)	850	(	96.4	)	32	(	3.6	)		174	(	19.7	)	708	(	80.3	)	
3	884	(	22.2	)	830	(	93.9	)	54	(	6.1	)		153	(	17.3	)	731	(	82.7	)	
4 or more	676	(	17.0	)	640	(	94.7	)	36	(	5.3	)		158	(	23.4	)	518	(	76.6	)	
Children in household													0.5846									0.9193
None	2081	(	52.4	)	1978	(	95.1	)	103	(	4.9	)		418	(	20.1	)	1663	(	79.9	)	
1 or more	1894	(	47.6	)	1793	(	94.7	)	101	(	5.3	)		378	(	20.0	)	1516	(	80.0	)	
Health status																						
Self-Rated Health													0.0955									<0.0001
Excellent	966	(	24.3	)	905	(	93.7	)	61	(	6.3	)		165	(	17.1	)	801	(	82.9	)	
Very good	1810	(	45.5	)	1730	(	95.6	)	80	(	4.4	)		321	(	17.7	)	1489	(	82.3	)	
Good/Fair/Poor	1199	(	30.2	)	1136	(	94.7	)	63	(	5.3	)		310	(	25.9	)	889	(	74.1	)	
Chronic Condition													0.8765									0.0023
None**	2728	(	68.6	)	2589	(	94.9	)	139	(	5.1	)		582	(	21.3	)	2146	(	78.7	)	

1 or more	1247	(	31.4	)	1182	(	94.8	)	65	(	5.2	)		214	(	17.2	)	1033	(	82.8	)	
Daily medications													0.5732									<0.0001
0	1931	(	48.6	)	1839	(	95.2	)	92	(	4.8	)		454	(	23.5	)	1477	(	76.5	)	
1	852	(	21.4	)	805	(	94.5	)	47	(	5.5	)		149	(	17.5	)	703	(	82.5	)	
2	533	(	13.4	)	499	(	93.6	)	34	(	6.4	)		90	(	16.9	)	443	(	83.1	)	
3	322	(	8.1	)	308	(	95.7	)	14	(	4.3	)		41	(	12.7	)	281	(	87.3	)	
4 or more	337	(	8.5	)	320	(	95.0	)	17	(	5.0	)		62	(	18.4	)	275	(	81.6	)	
Health behaviors																						
Smoking													0.9940									0.0035
Not current smoker	3099	(	78.0	)	2940	(	94.9	)	159	(	5.1	)		590	(	19.0	)	2509	(	81.0	)	
Smoke tobacco products	876	(	22.0	)	831	(	94.9	)	45	(	5.1	)		206	(	23.5	)	670	(	76.5	)	
Influenza vaccination history in past 5 years													<0.0001									<0.0001
No vaccination history	646	(	16.3	)	591	(	91.5	)	55	(	8.5	)		297	(	46.0	)	349	(	54.0	)	
1 - 3 years of vaccination	628	(	15.8	)	589	(	93.8	)	39	(	6.2	)		194	(	30.9	)	434	(	69.1	)	
4 or more years of vaccination	2701	(	67.9	)	2591	(	95.9	)	110	(	4.1	)		305	(	11.3	)	2396	(	88.7	)	
Potential virus exposures and use of PPE, Median (IQR) of Average Monthly Updates per Participant††																						
Hours within 3 feet of others at work	27	(	20.0-35.3	)	27	(	20.0-35.2	)	25	(	20.0-37.9	)	0.1031	26	(	20.0-35.6	)	27	(	20.0-35.2	)	0.1056
While in close contact at work, percent time using PPE ‡‡	99	(	90.0-100	)	99	(	90.0-100	)	100	(	89.0-100	)	0.6347	96	(	78.6-100	)	99	(	99.4-100	)	<0.0001
Hours within 3 feet of suspected or confirmed COVID-19 at work, home, or community	8	(	2.2-24.0	)	8	(	2.2-24.0	)	6	(	2.0-23.2	)	0.4463	10	(	3.1-26.7	)	7	(	2.0-23.4	)	0.0003

Abbreviations: Interquartile range (IQR), Healthcare personnel (HCP), First responders (FR), Essential and frontline workers (EFW), COVID-19-like illness (CLI); Messenger RNA (mRNA); Personal protective equipment (PPE)

*P-values calculated for categorical variables using Pearson's chi-squared test or Fisher's exact test for cells with <5 observations; Kruskal-Wallis non-parametric tests was used to compare median values.

† Analytic sample excludes 1,147 participants with documented SARS-CoV-2 infection before enrollment or as part of surveillance.

‡ Sites identified had higher percentages of their participants with RT-PCR-confirmed SARS-CoV-2 infections than the other sites Chi-square = 41.0, p-value <0.0001.

§ Comparison of those who were vaccinated with at least one dose and those who were not, cohort locations for Portland, OR, Duluth, MN, Salt Lake City UT were combined compared to Phoenix, AZ, Tucson, AZ, Other, AZ, Miami, FL and Temple, TX with chi-square value of 88.3 (p-value <0.0001).

‖ For 15 participants missing biological sex, it was imputed as the more common category (female).

¶ Occupation categories: Primary HCP (physicians, physician assistants, nurse practitioners, dentists), Other allied HCP (nurses, therapists, technicians, medical assistants, orderlies and all others providing clinical support in inpatient or outpatient settings), first responders (FR; firefighters, law enforcement, corrections, emergency medical technicians), essential and frontline workers (EFW; workers in hospitality, delivery, and retail; teachers; all other occupations that require contact within 3 feet of the public, customers, or co-workers as a routine part of their job).

** For 77 participants, who did not respond to the self-report question, they were imputed as none, pending further verification.

†† Each month, participants were asked about close contacts and PPE use during the past 7 days. The mean of monthly responses during the study period were calculated.

‡‡ Only applicable for participants indicating a potential exposure during the past 7 days.

Table_S3. Number and percentage of SARS-CoV-2 viruses by three lineage classifications and by vaccination status at infection and cohort location.

Whole genome sequencing was conducted at CDC using previously published protocols for SARS-CoV-2 viruses detected among 22 participants who were ≥7 days post-dose-1 at infection (through March 3, 2021) and among 3-4 unvaccinated participants at the same location with infection dates closest to the index case. Lineages were categorized as variants of concern, interest, or wild type/other by CDC website (Supplementary_Appendix_Methods).

	Variants of Concern		Variants of Interest		Wild Type & Other		
	N	Col. %	N	Col. %	N	Col. %	
Total	**10**		**1**		**82**		
By vaccination status at infection							Variants of concern / All (but not variant of interest)
Unvaccinated	7	70	1	100	63	77	7/70 (10%)
Indeterminate (days 1-13 post dose-1)	0	0	0	0	12	15	0/12 (0%)
Partially or fully vaccinated (≥14-days post dose-1)*	3	30	0	0	7	9	3/10 (30%)
By cohort location							
Phoenix, AZ	2	20	1	100	12	15	
Tucson, AZ	2	20	0	0	22	32	
Other, AZ	1	10	0	0	14	17	
Miami, FL	0	0	0	0	5	1	
Duluth, MN	0	0	0	0	7	9	
Portland, OR	0	0	0	0	2	2	
Temple, TX	1	10	0	0	10	12	
Salt Lake City, UT	4	40	0	0	10	12	
Month of detection							

December	1 (10)	0 (0)	34 (41)
January	5 (50)	1 (100)	38 (46)
February	3 (30)	0 (0)	10 (12)
March	1 (10)	0 (0)	0 (0)
April	0 (0)	0 (0)	0 (0)

By cohort location and unvaccinated vs. vaccinated (excluding 12 indeterminates; all wild type or other)

Phoenix, AZ			
Unvaccinated	2 (20)	1 (100)	9 (11)
Partially or fully vaccinated	0 (0)	0 (0)	2 (2)
Tucson, AZ			
Unvaccinated	1 (10)	0 (0)	18 (27)
Partially or fully vaccinated	1 (10)	0 (0)	1 (1)
Other, AZ			
Unvaccinated	1 (10)	0 (0)	10 (12)
Partially or fully vaccinated	0 (0)	0 (0)	2 (2)
Miami, FL			
Unvaccinated	0 (0)	0 (0)	4 (0)
Partially or fully vaccinated	0 (0)	0 (0)	0 (0)
Duluth, MN			
Unvaccinated	0 (0)	0 (0)	4 (5)
Partially or fully vaccinated	0 (0)	0 (0)	2 (2)
Portland, OR			
Unvaccinated	0 (0)	0 (0)	1 (1)
Partially or fully vaccinated	0 (0)	0 (0)	0 (0)
Temple, TX			
Unvaccinated	1 (10)	0 (0)	7 (9)
Partially or fully vaccinated	0 (0)	0 (0)	0 (0)

Salt Lake City, UT									
Unvaccinated	2	(	20	)	0	(	0	)	10	(	12	)
Partially or fully vaccinated	2	(	20	)	0	(	0	)	0	(	0	)
By lineage classification from sequencing												
B.1.429	8	(	80	)								
B.1.1.7	1	(	10	)								
B.1.427	1	(	10	)								
P.2					1	(	100	)				
B.1									9	(	11	)
B.1.1.231									1	(	1	)
B.1.1.316									4	(	5	)
B.1.1.434									1	(	1	)
B.1.2									42	(	51	)
B.1.234									1	(	1	)
B.1.239									2	(	2	)
B.1.243									6	(	7	)
B.1.400									2	(	2	)
B.1.409									1	(	1	)
B.1.517									1	(	1	)
B.1.551									5	(	6	)
B.1.565									1	(	1	)
B.1.587									1	(	1	)
B.1.596									4	(	5	)
B.1.609									1	(	1	)

*Among participants with variants of concern, 1 was partially vaccinated, 2 were fully vaccinated. Among participants with wild type and other variants, 6 were partially vaccinated and 1 was fully vaccinated

Table S4. Sensitivity analysis to main vaccine effectiveness (VE) estimates that eliminates person-time for those with potential vaccination or infection misclassification and during periods of low local virus circulation.

	Contributing Participants *	Total Person-Days	Median (IQR) Days	SARS-CoV-2 Infections	Unadjusted VE	Adjusted VE †
mRNA COVID-19 vaccination status					% (95% CI)	% (95% CI)
Unvaccinated	3,948	121,992	17 (8 - 40)	151		
Partially vaccinated (≥14-days post dose-1 to day 13 post dose-2)	2,995	80,638	22 (21 - 28)	11	87 (74 - 93)	81 (64 - 90)
Fully vaccinated (≥14-days post dose-2)	2,508	159,898	69 (52 - 81)	5	92 (80 - 97)	91 (77 - 97)

Abbreviations: Messenger RNA (mRNA), Vaccine effectiveness (VE), Interquartile range (IQR)

* Contributing participants in vaccination categories do not equal the number with each vaccination dose because participants must have met the vaccination criteria for each status category

† Adjusted VE is inversely weighted for propensity to be vaccinated with doubly robust adjustment for local virus circulation, study location, and occupation. This model excludes person-time among those presumed to be unvaccinated but lacking confirmation (n = 68), person-time after an indeterminate RT-PCR result (n = 5), and person-time during weeks of low local virus circulation (defined as no RT-PCR-confirmed infections within local cohort and percent positive of local SARS-CoV-2 testing fell below 3% for ≥5 days): Tucson, AZ suspended 3/28 to 4/5/21; Duluth, MN suspended 2/15 to 4/4/21; Portland, OR suspended 3/6 to 3/31/21. Also see Figure_S1.

Table S5. Participant characteristics by mRNA vaccine vaccination status at time of RT-PCR-confirmed SARS-CoV-2 infections.

	All SARS-CoV-2 RT-PCR-Positives		SARS-CoV-2 Positives by Vaccination Status at Infection									Partial and Full Vaccination Combined					
			Unvaccinated		Partially Vaccinated		Fully Vaccinated			p-value*		Unvaccinated		Any Vaccination			p-value*
	N	Col. %	N	Row %	N	Row %	N	Row %				N	Col. %	N	Col %		
All participants †	204		156	76.5	11	5.4	5	2.45				156	76.5	16	7.8		
Socio-demographic characteristics																	
Cohort location‡,§										0.0031							0.0182
Phoenix, AZ	43	8.5	32	74.4	3	7.0	0	0.0	‡			32	20.5	3	18.8	§	
Tucson, AZ	75	6.2	63	84.0	1	1.3	2	2.7	‡			63	40.4	3	18.8	§	
Other, AZ	15	5.2	9	60.0	1	6.7	1	6.7	‡			9	5.8	2	12.5	§	
Miami, FL	23	9.7	22	95.7	0	0.0	0	0.0	‡			22	14.1	0	0.0	§	
Duluth, MN	11	2.2	6	54.5	3	27.3	0	0.0				6	3.8	3	18.8		
Portland, OR	5	0.8	2	40.0	0	0.0	1	20.0				2	1.3	1	6.3		
Temple, TX	18	5.7	13	72.2	1	5.6	0	0.0	‡			13	8.3	1	6.3	§	
Salt Lake City, UT	14	3.0	9	64.3	2	14.3	1	7.1				9	5.8	3	18.8		
Sex										0.1713							0.063
Female	111	4.4	79	71.2	8	7.2	4	3.6				79	50.6	12	75.0		
Male	93	6.3	77	82.8	3	3.2	1	1.1				77	49.4	4	25.0		
Age (Years)										0.8332							0.5969
18-49	142	4.9	107	75.4	8	5.6	4	2.8				107	68.6	12	75.0		
≥50	62	5.5	49	79.0	3	4.8	1	1.6				49	31.4	4	25.0		
Race										0.6995							0.4014
White	178	5.1	138	77.5	9	5.1	4	2.2				138	88.5	13	81.3		
Other	26	5.1	18	69.2	2	7.7	1	3.8				18	11.5	3	18.8		
Ethnicity										0.1861							0.1216
Hispanic/Latinx	60	8.5	40	66.7	4	6.7	3	5.0				40	25.6	7	43.8		

Other	144	(	4.4	)	116	(	80.6	)	7	(	4.9	)	2	(	1.4	)		116	(	74.4	)	9	(	56.3	)	
Occupation[l]																	0.0257									0.0278
Primary HCP	16	(	2.0	)	8	(	50.0	)	3	(	18.8	)	0	(	0.0	)		8	(	5.1	)	3	(	18.8	)	
Nurses and other allied HCP	66	(	4.9	)	45	(	68.2	)	6	(	9.1	)	2	(	3.0	)		45	(	28.8	)	8	(	50.0	)	
First Responders	73	(	9.2	)	62	(	84.9	)	1	(	1.4	)	2	(	2.7	)		62	(	39.7	)	3	(	18.8	)	
Essential and other frontline	49	(	4.5	)	41	(	83.7	)	1	(	2.0	)	1	(	2.0	)		41	(	26.3	)	2	(	12.5	)	
Chronic Condition																	0.5743									0.7371
None [¶]	139	(	5.1	)	104	(	74.8	)	6	(	4.3	)	4	(	2.9	)		104	(	66.7	)	10	(	62.5	)	
1 or more	65	(	5.1	)	52	(	80.0	)	5	(	7.7	)	1	(	1.5	)		52	(	33.3	)	6	(	37.5	)	
Potential exposures to virus from monthly reports, Median (IQR)**																	0.3571									0.1723
Average hours worked in direct contact with coworkers	25	(	20.0-37.9	)	25	(	20.0-38.9	)	20	(	20.0-26.2	)	28	(	20.0-28.4	)		25	(	20.0-38.9	)	20	(	20.0-28.4	)	
Average hours of direct contact with suspected or confirmed SARS-CoV-2 infection	6	(	2.0-23.2	)	8	(	2.0-20.0	)	3	(	2.2-3.6	)	18.8	(	2.6-30.4	)	0.5449	8	(	2.0-20.0	)	3	(	2.2-30.0	)	0.6364
Use of personal protective equipment (PPE) from monthly reports																										
PPE use during work [††]																	N/A									N/A
No	0	(	0.0	)	0	(	0.0	)	0	(	0.0	)	0	(	0.0	)		0	(	0.0	)	0	(	0.0	)	
Yes	163	(	79.9	)	123	(	75.5	)	10	(	6.1	)	5	(	3.1	)		123	(	78.8	)	15	(	93.8	)	
Missing	41				33				1				0													
PPE use at work, community, home [††]																	0.0532									0.0202
No close SARS-CoV-2 contact in past 7 days	84	(	41.2	)	66	(	78.6	)	2	(	2.4	)	0	(	0.0	)		66	(	42.3	)	2	(	12.5	)	

Close contact and use PPE above 100% of the time	0	(	0.0	)	0	(	0.0	)	0	(	0.0	)	0	(	0.0	)	0	(	0.0	)	0	(	0.0	)
Close contact and use PPE ≤ 100% of the time	120	(	58.8	)	90	(	75.0	)	9	(	7.5	)	5	(	4.2	)	90	(	57.7	)	14	(	87.5	)

Abbreviations: Interquartile range (IQR), Healthcare personnel (HCP), First responders (FR), Essential and frontline workers (EFW), COVID-19-like illness (CLI); Messenger RNA (mRNA); Not applicable (N/A)

*P-values calculated using Pearson's chi-squared test or Fisher's exact test for cells with <5 observations; Kruskal Wallis non-parametric tests was used to compare median values.

† Analytic sample excludes 1,147 participants with documented SARS-CoV-2 infection before enrollment or as part of surveillance prior to the study period. Socio-demographic information was collected by self-report as part of an electronic enrollment survey.

‡ Comparison of the three vaccination groups, cohort locations for Portland, OR, Duluth, MN, Salt Lake City UT were combined compared to Phoenix, AZ, Tucson, AZ, Other, AZ, Miami, FL and Temple, TX with chi-square value of 13.1 (p-value 0.0014)

§ Comparison of any vaccination versus unvaccinated, cohort locations for Portland, OR, Duluth, MN, Salt Lake City UT were combined and compared to Phoenix, AZ, Tucson, AZ, Other, AZ, Miami, FL and Temple, TX with chi-square value of 13.0 (p-value 0.0003)

‖ Occupation categories: Primary HCP (physicians, physician assistants, nurse practitioners, dentists), Other allied HCP (nurses, therapists, technicians, medical assistants, orderlies and all others providing clinical support in inpatient or outpatient settings), first responders (FR; firefighters, law enforcement, corrections, emergency medical technicians), essential and frontline workers (EFW; workers in hospitality, delivery, and retail; teachers; all other occupations that require contact within 3 feet of the public, customers, or co-workers as a routine part of their job)

¶ For 7 participants, who did not respond to the self-report question, they were imputed as none, pending further verification.

**Each month, participants were asked about close contacts and PPE use during the past 7 days. The mean of monthly responses during the study period were calculated.

‡ ‡ Only applicable for participants indicating a potential exposure during the past 7 days.

Table S6. Indicators of potential vaccine attenuation by participant characteristics among those with RT-PCR-confirmed SARS-CoV-2 infection.

	All SARS-CoV-2 RT-PCR-Positives		Viral RNA Load, Log10 Copies/mL			Symptom Duration			Days in Bed			Febrile CLI		Afebrile CLI**			RT-PCR Positive >2 weeks		RT-PCR Positive 1 week		
	N	Col %	Mean	SD	p-value	Mean	SD	p-value	Mean	SD	p-value	N	Col. %	N	Col %	p-value*	N	Col. %	N	Col %	p-value*
All participants †	204		3.6	1.7		15.3	14.4		3.2	5.3		116	56.9	88	43.1		135	66.2	69	33.8	
Socio-demographic characteristics																					
Cohort location‡,§					0.6966			0.0029			0.1017					0.0025				0.8252
Phoenix, AZ	43	8.5	3.3	1.7		18.2	11.3		4.7	8.7		24	20.7	19	21.6		30	22.2	13	9.6	
Tucson, AZ	75	6.2	3.7	1.7		16.6	14.6		2.9	3.3		52	44.8	23	26.1		50	37.0	25	18.5	
Other, AZ	15	5.2	3.4	2		14.2	14.2		2.7	3.3		9	7.8	6	6.8		11	8.1	4	3.0	
Miami, FL	23	9.7	3.7	1.6		15	22.4		2.5	4.2		9	7.8	14	15.9		14	10.4	9	6.7	
Duluth, MN	11	2.2	3.9	1.6		15.5	15.6		5.2	8.9		9	7.8	2	2.3		9	6.7	2	1.5	
Portland, OR	5	0.8	3.7	2.3		17.4	7		4.6	1.7		3	2.6	2	2.3		3	2.2	2	1.5	
Temple, TX	18	5.7	3.6	2.1		8.9	10.6		1.6	2.3		8	6.9	10	11.4		10	7.4	8	5.9	
Salt Lake City, UT	14	3.0	4.3	1.2		8.7	7.3		1.9	3.2		2	1.7	12	13.6		8	5.9	6	4.4	
Sex					0.1489			0.8845			0.2974					0.7511				0.105
Female	111	4.4	3.5	1.7		14.8	12.5		3.8	6.4		62	53.4	49	55.7		68	50.4	43	31.9	
Male	93	6.3	3.8	1.7		16	16.4		2.5	3.5		54	46.6	39	44.3		67	49.6	23	17.0	
Age(Years)					0.5757			0.9234			0.4347					0.8189				0.7548
18-49	142	4.9	3.7	1.7		14.6	12.4		3.3	5.9		80	69.0	62	70.5		93	68.9	49	36.3	
≥50	62	5.5	3.5	1.7		17	18.1		3	3.8		36	31.0	26	29.5		42	31.1	20	14.8	
Race					0.6455			0.8889			0.9613					0.6063				0.062
White	178	5.1	3.6	1.6		15	13.9		3,3	5.6		100	86.2	78	88.6		122	90.4	56	41.5	
Other	26	5.1	3.7	1.7		17.3	17.4		2.6	2.7		16	13.8	10	11.4		13	9.6	13	9.6	
Ethnicity					0.7638			0.7932			0.0900					0.068				0.1264
Hispanic/Latinx	60	8.5	3.7	1.6		16	15		3.9	5.4		40	34.5	20	22.7		35	25.9	25	18.5	
Other	144	4.4	3.6	1.7		15.1	14.2		2.9	5.3		76	65.5	68	77.3		100	74.1	44	32.6	

Occupation[‖]					0.0254				0.9637				0.4043				0.7307					0.6604
Primary HCP	16	(2.0)	3.5	(1.7)		13.8	(10.9)		1.3	(1.3)		8	(6.9)	8	(9.1)		11	(8.1)	5	(3.7)	
Nurses and other allied HCP	66	(4.9)	3.3	(1.8)		14.9	(11.9)		3.5	(4.8)		37	(31.9)	29	(33.0)		40	(29.6)	26	(19.3)	
First Responders	73	(9.2)	4.1	(1.5)		15.2	(15.2)		2.9	(4.2)		45	(38.8)	28	(31.8)		49	(36.3)	24	(17.8)	
Essential and other frontline	49	(4.5)	3.4	(1.8)		16.6	(17.2)		3.8	(7.6)		26	(22.4)	23	(26.1)		35	(25.9)	14	(10.4)	
Chronic Condition					0.3464				0.6684				0.5598				0.2295					0.1133
None [¶]	139	(5.1)	3.5	(1.8)		15.4	(14.2)		3.1	(5.7)		83	(71.6)	56	(63.6)		87	(64.4)	52	(38.5)	
1 or more	65	(5.1)	3.7	(1.7)		15.1	(14.9)		3.3	(4)		33	(28.4)	32	(36.4)		48	(35.6)	17	(12.6)	

Abbreviations: Interquartile range (IQR), Healthcare personnel (HCP), First responders (FR), Essential and frontline workers (EFW), COVID-19-like illness (CLI); Messenger RNA (mRNA)

*P-values calculated using Pearson's chi-squared test or Fisher's exact test for cells with <5 observations; Kruskal Wallis non-parametric tests was used to compare median values.

† Analytic sample excludes 1,147 participants with documented SARS-CoV-2 infection before enrollment or as part of surveillance prior to the study period. Socio-demographic information was collected by self-report as part of an electronic enrollment survey.

‡ Comparison of the three vaccination groups, cohort locations for Portland, OR, Duluth, MN, Salt Lake City UT were combined compared to Phoenix, AZ, Tucson, AZ, Other, AZ, Miami, FL and Temple, TX with chi-square value of 13.1 (p-value 0.0014)

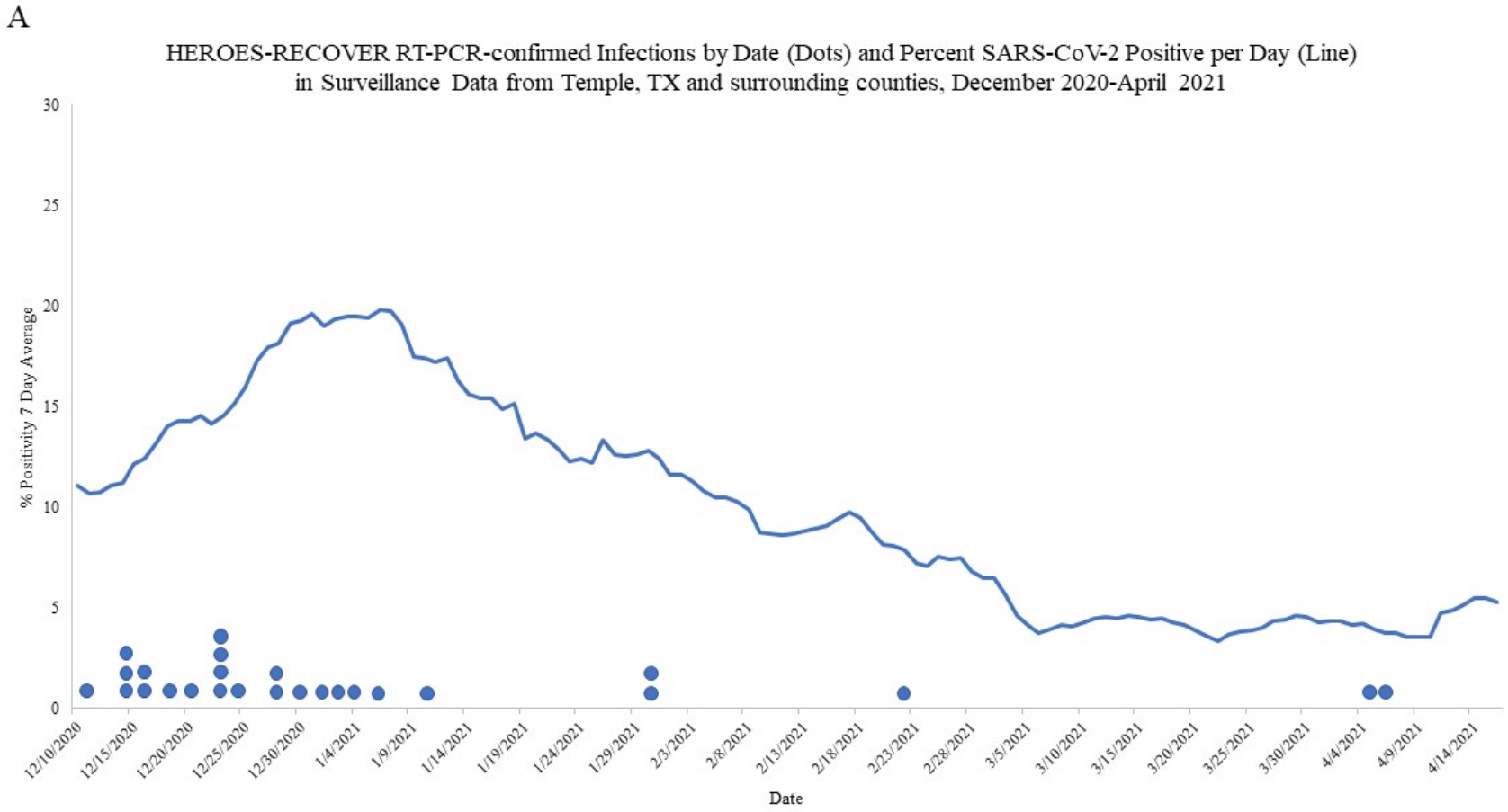
§ Comparison of any vaccination versus unvaccinated, cohort locations for Portland, OR, Duluth, MN, Salt Lake City UT were combined and compared to Phoenix, AZ, Tucson, AZ, Other, AZ, Miami, FL and Temple, TX with chi-square value of 13.0 (p-value 0.0003)

‖ Occupation categories: Primary HCP (physicians, physician assistants, nurse practitioners, dentists), Other allied HCP (nurses, therapists, technicians, medical assistants, orderlies and all others providing clinical support in inpatient or outpatient settings), first responders (FR; firefighters, law enforcement, corrections, emergency medical technicians), essential and frontline workers (EFW; workers in hospitality, delivery, and retail; teachers; all other occupations that require contact within 3 feet of the public, customers, or co-workers as a routine part of their job)

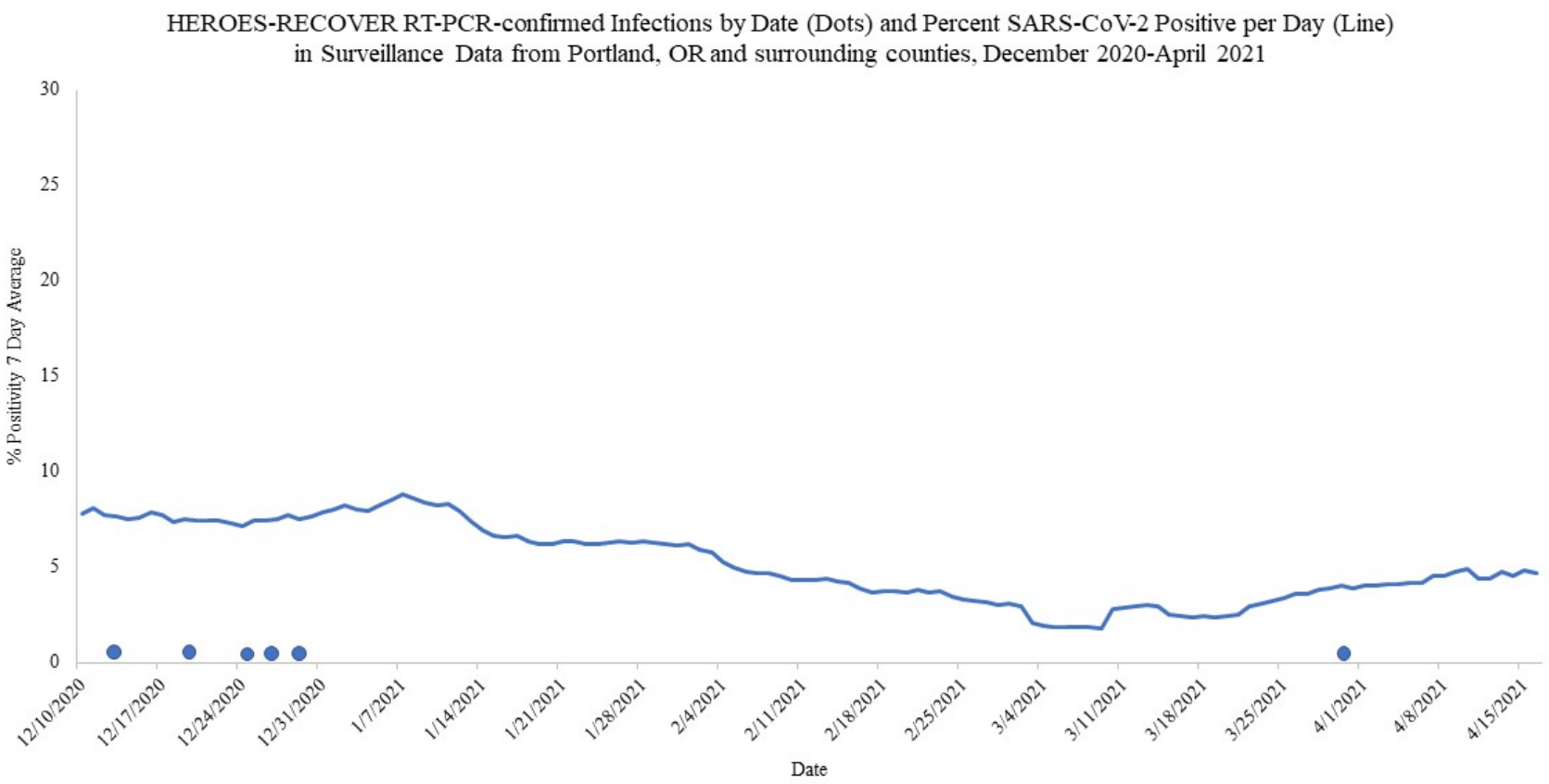
¶ For 7 participants, who did not respond to the self-report question, they were imputed as none, pending further verification.

**Afebrile defined as anyone who didn't report fever or chills in surveys

Figure_S1. Percent SARS-CoV-2 positive of all tested in local counties and dates of PCR-confirmed infections by site location (panels A-H)

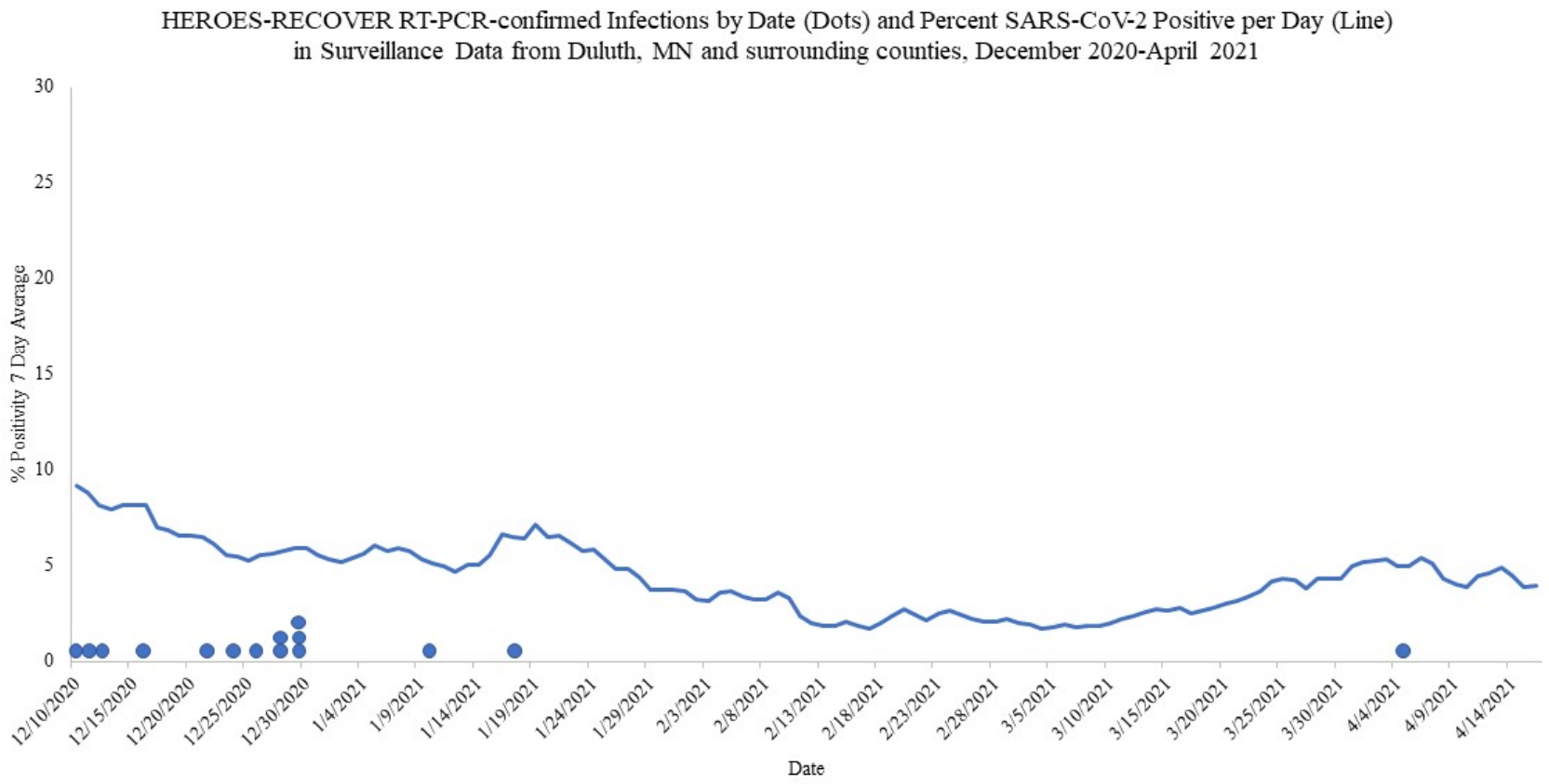


B



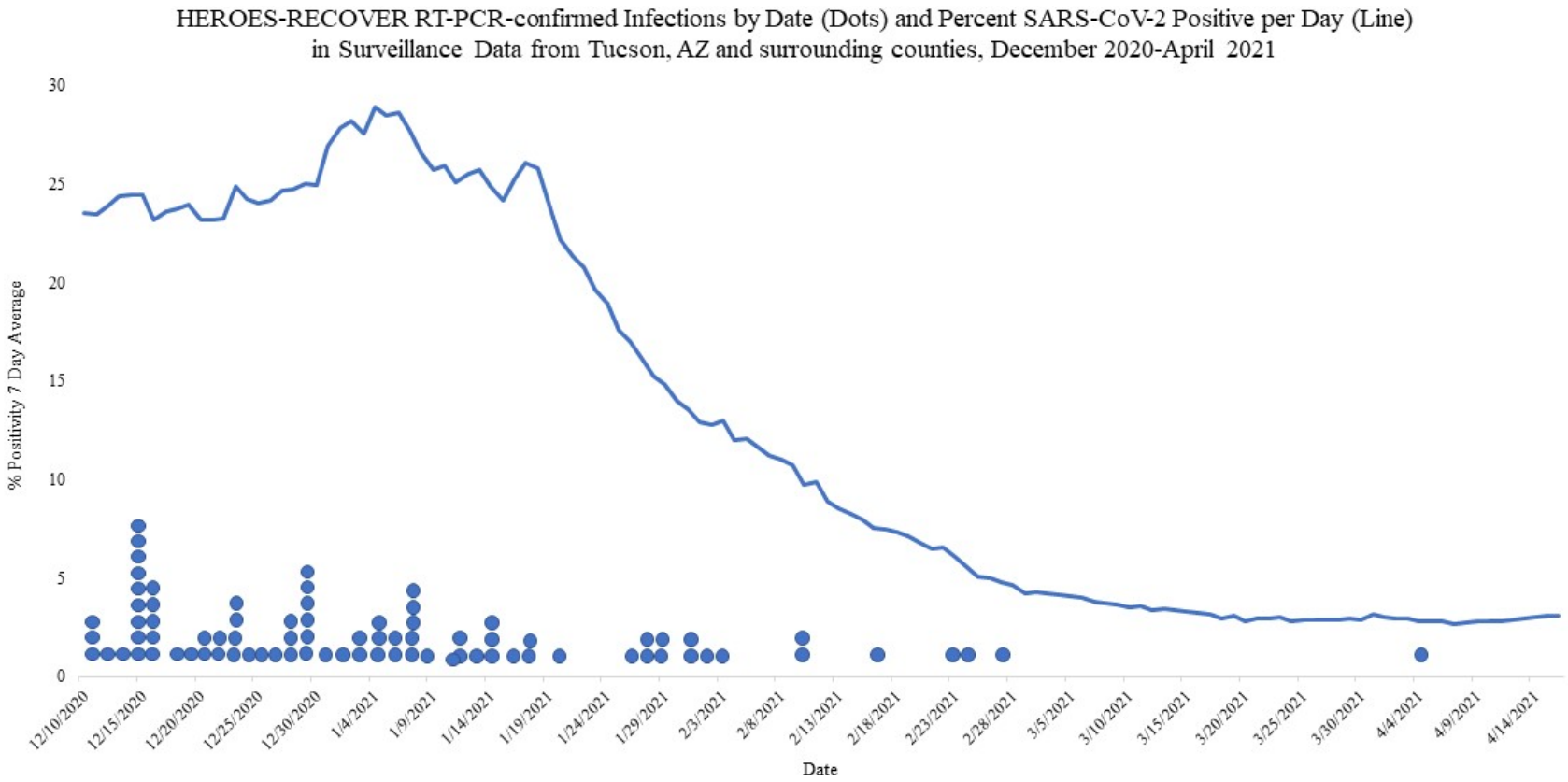
Percent Positivity 7 Day average is from Clackamas, Multnomah and Washington Counties, OR and obtained from https://protect.hhs.gov/

C



Percent Positivity 7 Day average is from Carlton, Douglas, Lake and St. Louis Counties, MN as well as Ashland and Bayfield Counties, WI. Data was obtained from https://protect.hhs.gov

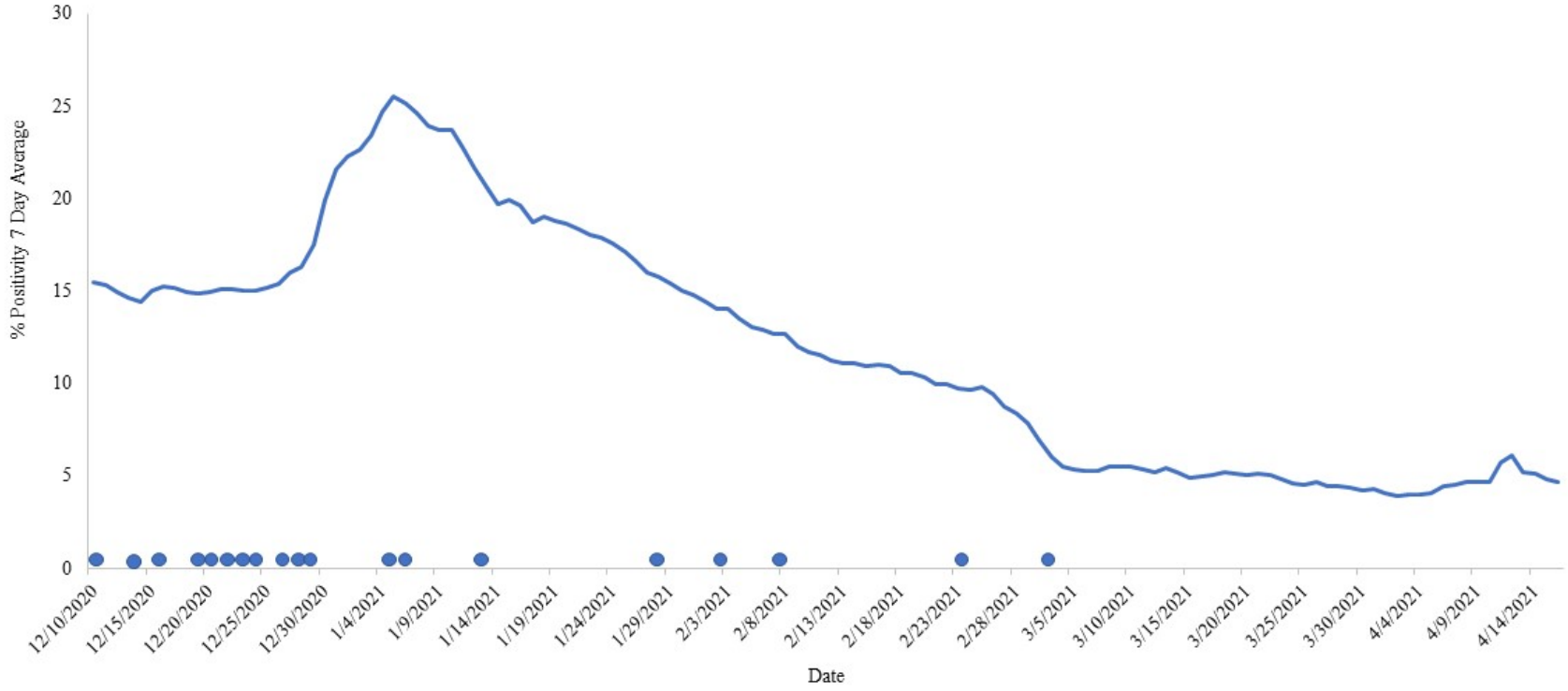
D



Percent Positivity 7 Day average is from Pima County, AZ and obtained from https://protect.hhs.gov

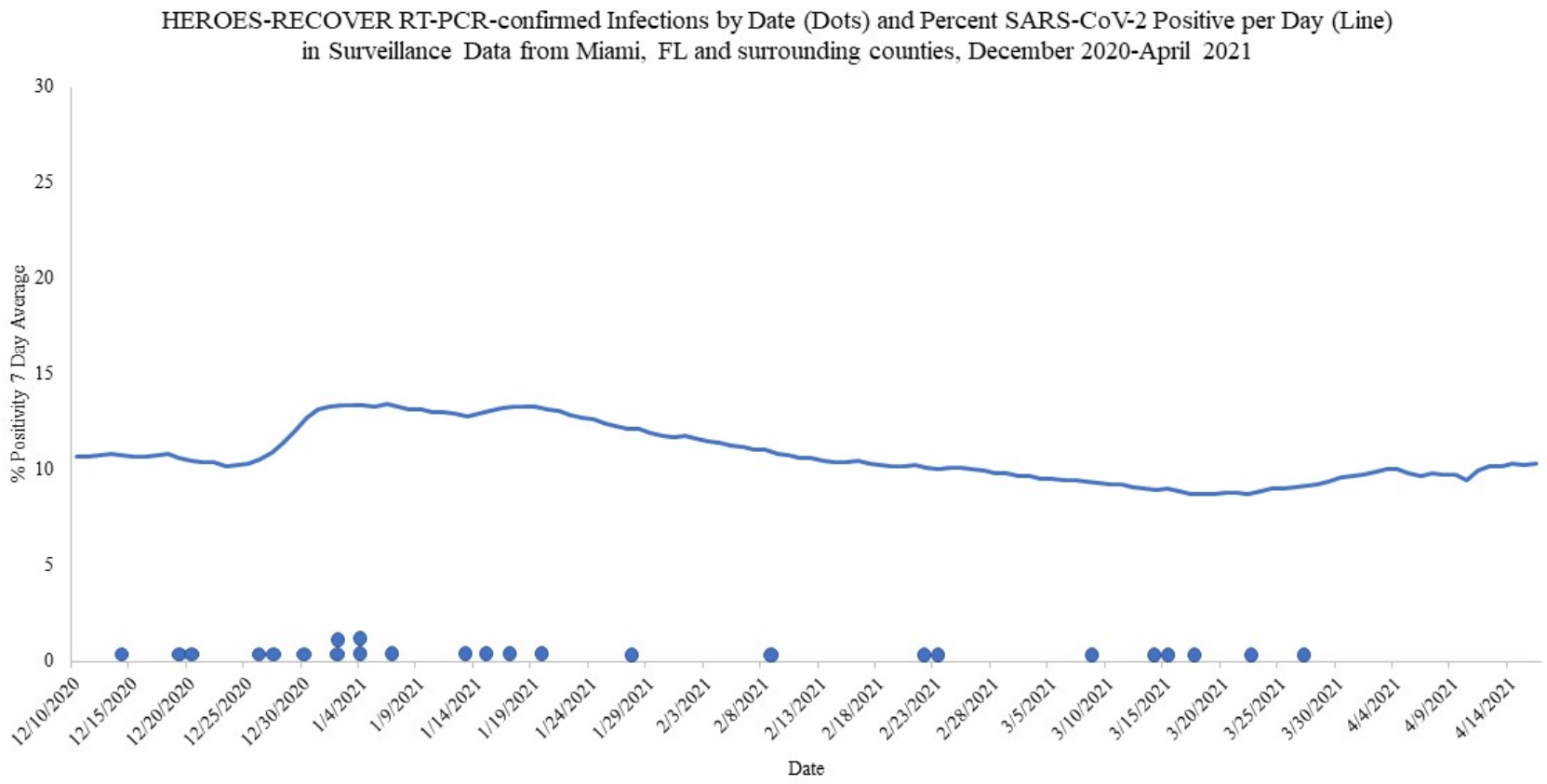
E

HEROES-RECOVER RT-PCR-confirmed Infections by Date (Dots) and Percent SARS-CoV-2 Positive per Day (Line) in Surveillance Data from Salt Lake City, UT and surrounding counties, December 2020-April 2021



Percent Positivity 7 Day average is from Davis, Salt Lake, Summit, Tooele, Utah and Weber Counties, UT and obtained from https://protect.hhs.gov

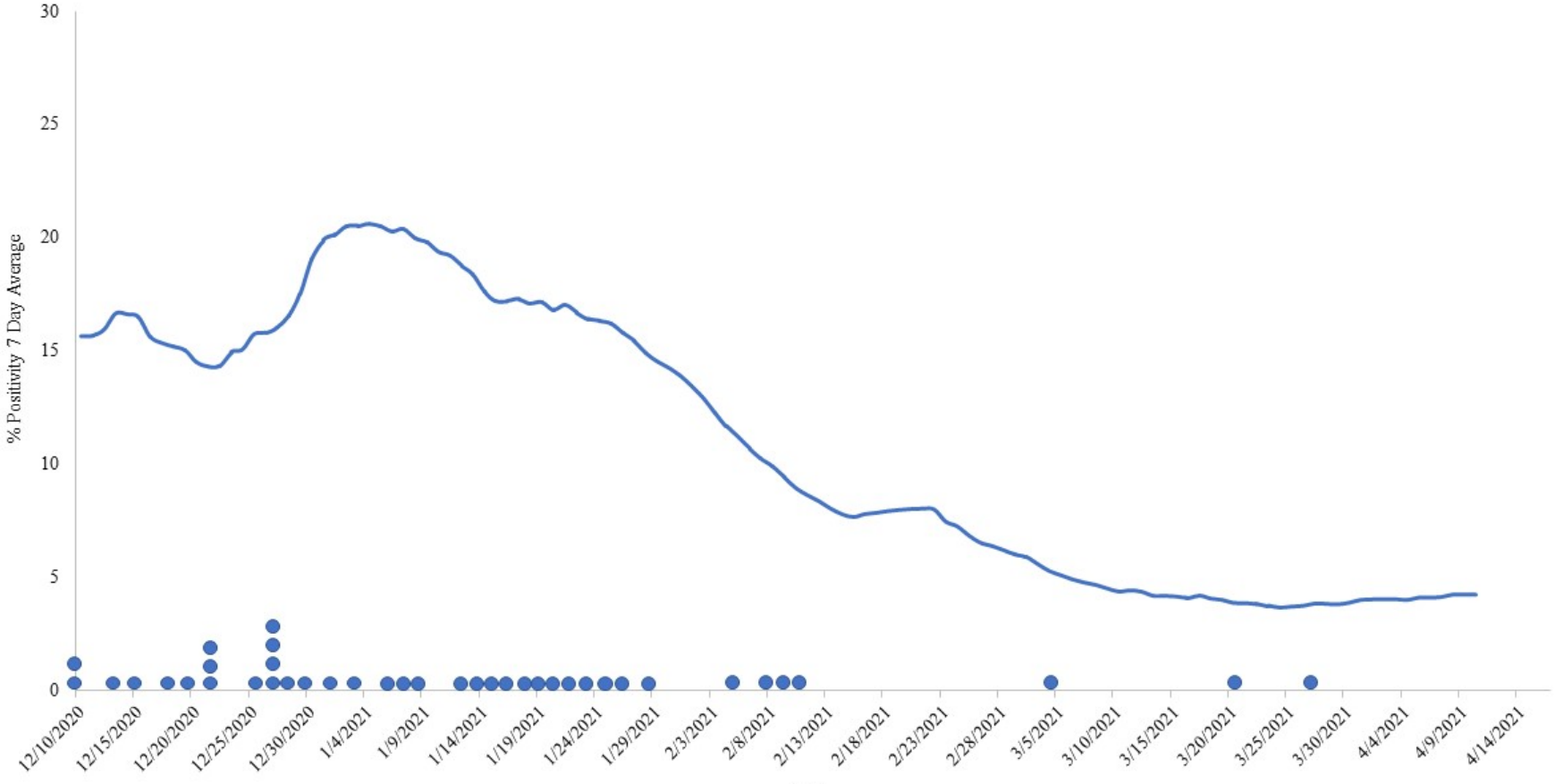
F



Percent Positivity 7 Day average is from Broward, Miami-Dade and Palm Beach Counties, FL and obtained from https://protect.hhs.gov

G

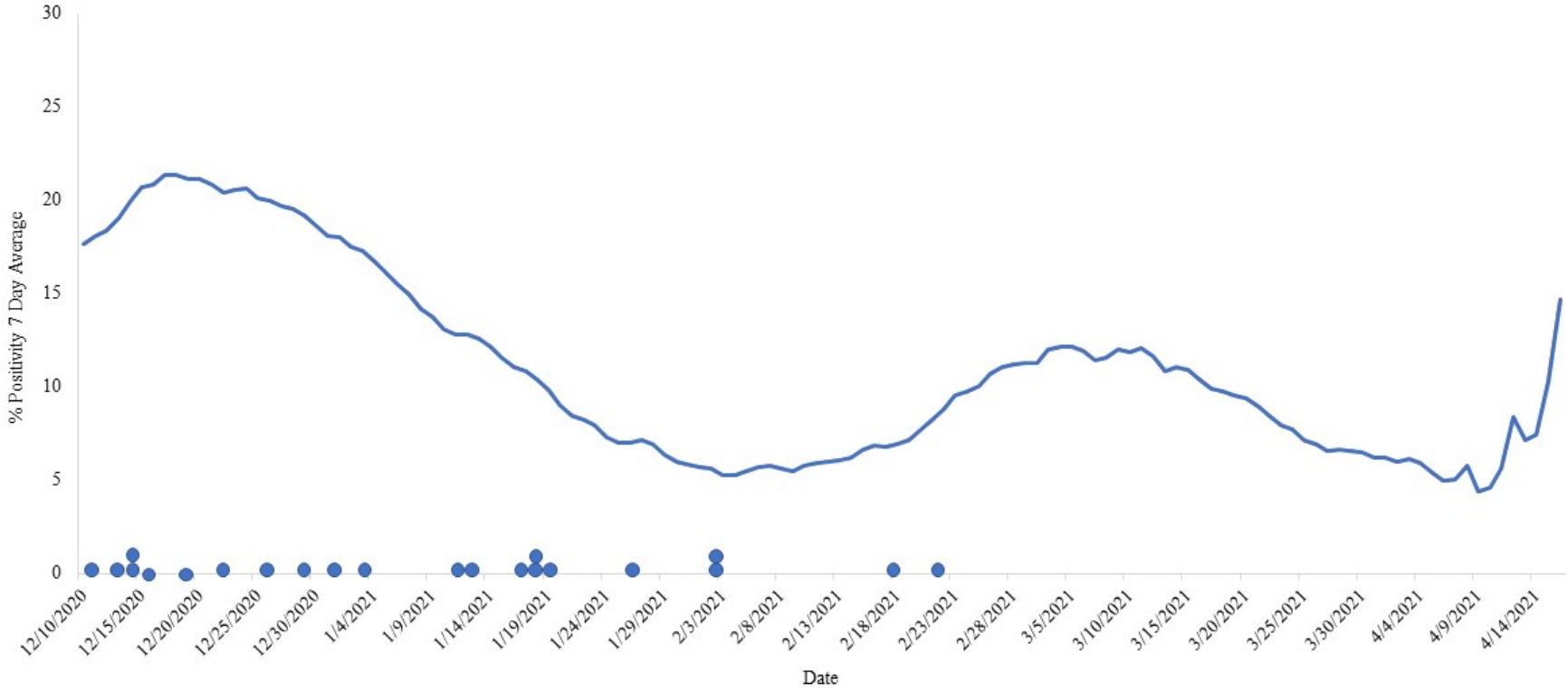
HEROES-RECOVER RT-PCR-confirmed Infections by Date (Dots) and Percent SARS-CoV-2 Positive per Day (Line) in Surveillance Data from Phoenix, AZ and surrounding counties, December 2020-April 2021



Percent Positivity 7 Day average is from Maricopa County, AZ and obtained from https://protect.hhs.gov

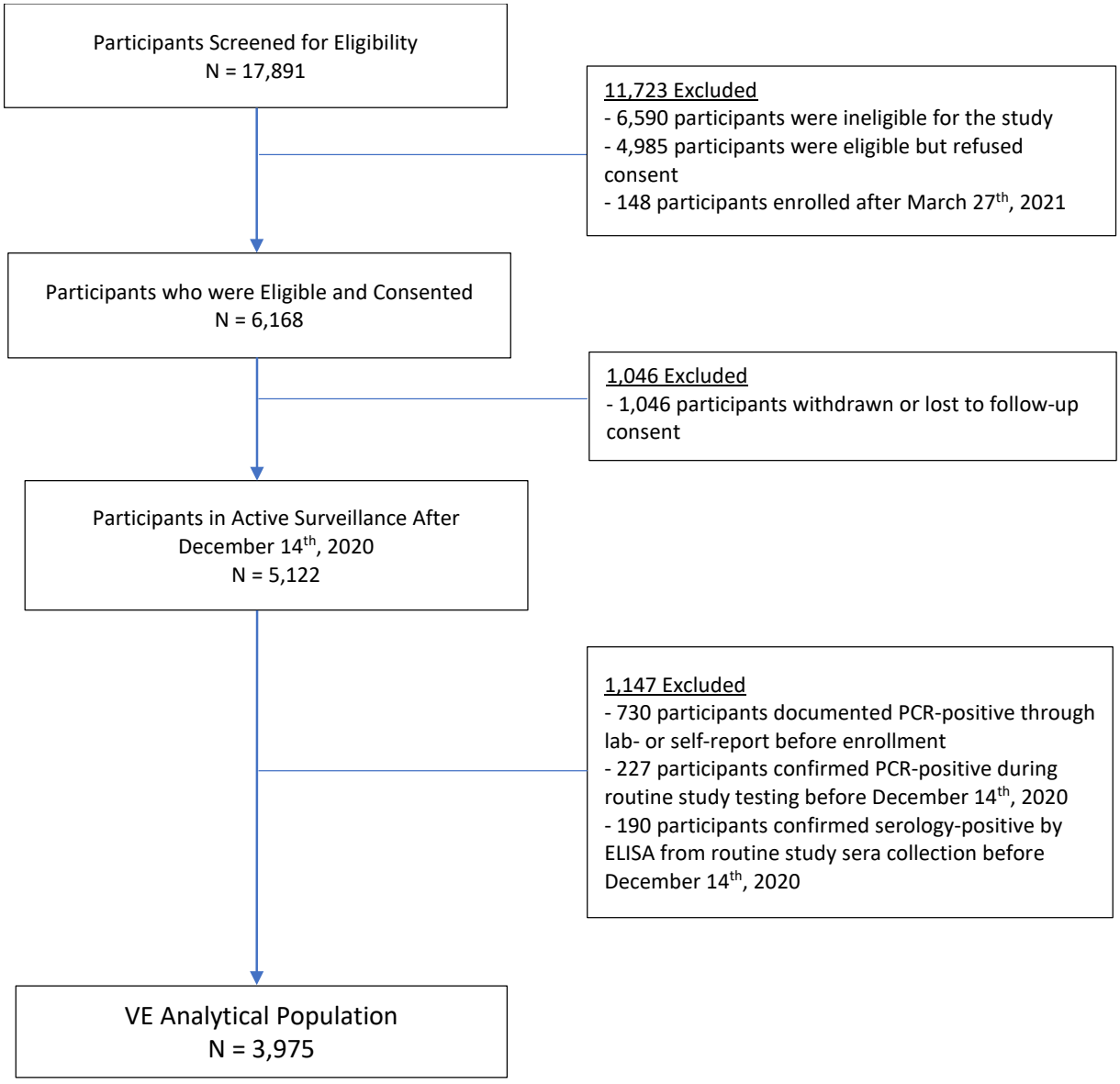
H

HEROES-RECOVER RT-PCR-confirmed Infections by Date (Dots) and Percent SARS-CoV-2 Positive per Day (Line) in Surveillance Data from Other AZ, December 2020-April 2021



Percent Positivity 7 Day average is from Apache, Cochise, Coconino, Gila, Graham, Greenlee, La Paz, Mohave, Navajo, Pinal, Santa Cruz, Yavapai, and Yuma Counties, AZ and obtained from https://protect.hhs.gov

Figure S2. CONSORT diagram of HEROES-RECOVER prospective cohort participants

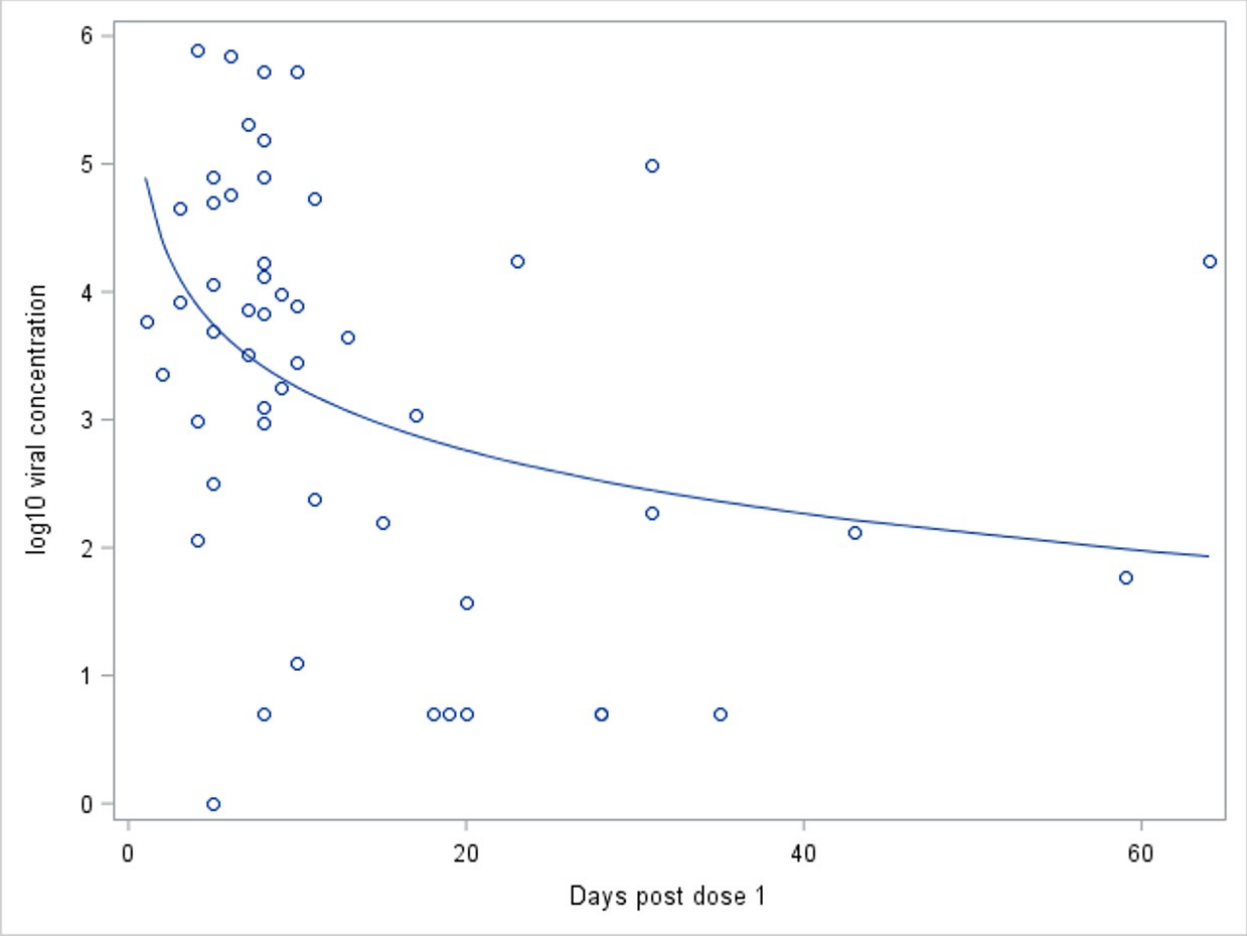


Figure_S3. Standardized mean differences of covariates between unvaccinated and vaccinated participants with receipt of at least one dose before and after inverse propensity of treatment weighting.

Legend: Negative differences indicate groups that are less likely to be vaccinated and positive differences indicate those more likely to be vaccinated. Absolute standard mean differences of less than 0.2 are considered well balanced. The largest difference after ATE weighting was 0.09.

Abbreviation: Average treatment effect weighted (ATE)

Figure_S4. SARS-CoV-2 viral RNA load among all participants with RT-PCR-confirmed infection after receipt of one dose of mRNA vaccine (n=50), by day post dose 1



REFERENCES

1. Roberts JD, Dickinson KL, Koebele E, et al. Clinicians, cooks, and cashiers: Examining health equity and the COVID-19 risks to essential workers. Toxicology and industrial health 2020;36(9):689-702.
2. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform 2019;95:103208. DOI: 10.1016/j.jbi.2019.103208.
3. Wagner AL, Gordon A, Tallo VL, et al. Intent to obtain pediatric influenza vaccine among mothers in four middle income countries. Vaccine 2020;38(27):4325-4335. DOI: https://doi.org/10.1016/j.vaccine.2020.04.028.
4. Hirsch A, Katz MA, Laufer Peretz A, et al. Study of Healthcare Personnel with Influenza and other Respiratory Viruses in Israel (SHIRI): study protocol. BMC Infect Dis 2018;18(1):550. doi: 10.1186/s12879-018-3444-7. (Clinical Trial).
5. (IATA) IATA. Dangerous Goods Regulations. 62 ed2021.
6. Prevention CfDCa. CDC 2019 Novel Coronavirus (2019-nCoV) Real-Time Reverse Transcriptase (RT)–PCR Diagnostic Panel. (https://www.cdc.gov/coronavirus/2019-ncov/lab/virus-requests.html).
7. Centers for Disease Control and Prevention. Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens for COVID-19. (https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html).
8. Ripperger TJ, Uhrlaub JL, Watanabe M, et al. Orthogonal SARS-CoV-2 Serological Assays Enable Surveillance of Low-Prevalence Communities and Reveal Durable Humoral Immunity. Immunity 2020;53(5):925-933 e4. DOI: 10.1016/j.immuni.2020.10.004.
9. Austin PC. Generating survival times to simulate Cox proportional hazards models with time-varying covariates. Stat Med 2012;31(29):3946-58. DOI: 10.1002/sim.5452.
10. FDA. TaqPath™ COVID-19 Combo Kit. In vitro diagnostics EUAs. US Department of Health and Human Services, Food and Drug Administration, 2020.
11. Paden CR, Tao Y, Queen K, et al. Rapid, Sensitive, Full-Genome Sequencing of Severe Acute Respiratory Syndrome Coronavirus 2. Emerg Infect Dis 2020;26(10):2401-2405. (In eng). DOI: 10.3201/eid2610.201800.
12. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11(5):550-60. (In eng). DOI: 10.1097/00001648-200009000-00011.
13. Therneau TM GP. Modeling survival data: Extending the Cox model. New York: Springer, 2000.
14. Naleway AL, Ball S, Kwong JC, et al. Estimating Vaccine Effectiveness Against Hospitalized Influenza During Pregnancy: Multicountry Protocol for a Retrospective Cohort Study. JMIR Res Protoc 2019;8(1):e11333. (In eng). DOI: 10.2196/11333.